THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HUGHES B. de THE,
AGNES MARCHIO,
PIERRE TIOLLAIS, and
ANNE DEJEAN

MAILED

MAY 12 1998

PAT.&T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 94-1465
Application 07/649,342[1]

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and WEIMAR, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

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[1] Application for patent filed February 1, 1991. According to appellants, the application is a continuation of Application 07/278,136, filed November 30, 1988, now abandoned; which is a continuation-in-part of Application 07/209,009, filed June 30, 1988, now Patent No. 5,149,781; which is a continuation-in-part of Application 07/134,130, filed December 17, 1987, now Patent No. 5,223,606; which is a continuation-in-part of Application 07/133,687, filed December 16, 1987, now abandoned.

REMAND TO THE EXAMINER

Our consideration of this record leads us to conclude that this case is not in condition for a decision on appeal. Accordingly, we remand the application to the examiner to consider the following issues and take appropriate action.

Representative Claims

Claims 1, 11, 24, 32, 53, 54, and 57 are illustrative of the subject matter on appeal and read as follows:

1. A cloned DNA sequence of hap gene, wherein the sequence has the formula:

ATGTTTGACTGTATGGATGTTCTGTCAGTGAGTCCTGGGCAAATCCTGGATTTCTACACTGCGAGT
CCGTCTTCCTGCATGCTCCAGGAGAAAGCTCTCAAAGCATGCTTCAGTGGATTGACCCAAACCGAA
TGGCAGCATCGGCACACTGCTCAATCAATTGAAACACAGAGCACCAGCTCTGAGGAACTCGTCCCA
AGCCCCCCATCTCCACTTCCTCCCCCTCGAGTGTACAAACCCTGCTTCGTCTGCCAGGACAAATCA
TCAGGGTACCACTATGGGGTCAGCGCCTGTGAGGGATGTAAGGGCTTTTTCCGCAGAAGTATTCAGA
AGAATATGATTTACACTTGTCACCGAGATAAGAACTGTGTTATTAATAAAGTCACCAGGAATCGAT
GCCAATACTGTCGACTCCAGAAGTGCTTTGAAGTGGGAATGTCCAAAGAATCTGTCAGGAATGACA
GGAACAAGAAAAAGAAGGAGACTTCGAAGCAAGAATGCACAGAGAGCTATGAAATGACAGCTGAGT
GTAAATACACCACGAATTCCAGTGCTGACCATCGAGTCCGACTGGACCTGGGCCTCTGGGACAAAT

TCAGTGAACTGGCCACCAAGTGCATTATTAAGATCGTGGAGTTTGCTAAACGTCTGCCTGGTTTCA

CTGGCTTGACCATCGCAGACCAAATTACCCTGCTGAAGGCCGCCTGCCTGGACATCCTGATTCTTA

GAATTTGCACCAGGTATACCCCAGAACAAGACACCATGACTTTCTCAGACGGCCTTACCCTAAATC

GAACTCAGATGCACAATGCTGGATTTGGTCCTCTGACTGACCTTGTGTTCACCTTTGCCAACCAGC

TCCTGCCTTTGGAAATGGATGACACAGAAACAGGCCTTCTCAGTGCCATCTGCTTAATCTGTGGAG

ACCGCCAGGACCTTGAGGAACCGACAAAAGTAGATAAGCTACAAGAACCATTGCTGGAAGCACTAA

AAATTTATATCAGAAAAAGACGACCCAGCAAGCCTCACATGTTTCCAAAGATCTTAATGAAAATCA

CAGATCTCCGTAGCATCAGTGCTAAAGGTGCAGAGCGTGTAATTACCTTGAAAATGGAAATTCCTG

GATCAATGCCACCTCTCATTCAAGAAATGATGGAGAATTCTGAAGGACATGAACCCTTGACCCCAA

GTTCAAGTGGGAACACAGCAGAGCACAGTCCTAGCATCTCACCCAGCTCAGTGGAAAACAGTGGGG

TCAGTCAGTCACCACTCGTGCAATAA,

wherein said DNA is in an isolated and purified form and encodes a retinoic acid receptor comprising a DNA binding domain and a hormone binding domain.

11. A hybrid duplex molecule consisting essentially of the DNA sequence of claim 1 hydrogen bonded to a nucleotide sequence of complementary base sequence.

24. A process for selecting a nucleotide sequence coding for hap protein or a portion thereof encoding a polypeptide capable of binding retinoic acid and functioning as a receptor from a group of nucleotide sequences comprising the step of determining which of said nucleotide sequences hybridizes to a DNA sequence as claimed in claim 1.

32. Plasmid pCOD20.

53. A recombinant DNA molecule comprising a DNA sequence of coding for a retinoic acid receptor, said DNA sequence coding on expression in a unicellular host for a polypeptide displaying the retinoic acid and DNA binding properties of RAR-β and being operatively linked to an expression control sequence in said DNA molecule.

54. Plasmid pPROHAP.

57. A DNA fragment comprising a portion of a DNA sequence, wherein the DNA sequence encodes a polypeptide of hap gene, and the DNA fragment comprises a nucleotide sequence selected from the group consisting of sequences:

(a) GTCAGGAATGACAGGAACAAGAAAAAGAAGGAGACTTCGAAGCAAGAATGC;

(b) GCTGAGTTGGAGATCTCACAGAGAAGATCCGA;

(c) GGGGTCAGTCAGTCACCACTCGTGCAA;

(d) AATGACAGGAACAAGAAAAAGAAGGAGACT;

(e) ATGTTTGACTGTATGGATGTTCTGTCAGTGAGTCCTGGGCAAATCCTGGATTT CTACACTGCG
AGTCCGTCTTCCTGCATGCTCCAGGAGAAAGCTCTCAAAGCATGCTTCAGTGGATTGACCCAAACCG GAA
TGGCAGCATCGGCACACTGCTCAATCA; and

(f) CATGAACCCTTGACCCCAAGTTCAAGTGGGAACACAGCAGAGCACAGTCCTAG CATCTCACCC
AGCTCAGTGGAAAACAGTGGGGTCAGTCAGTCACCACTCGTGCAA,

wherein sequence (a) encodes amino acid residues 151 to 167, sequence (b) encodes amino acid residues 175 to 185, sequence (c) encodes amino acid residues 440 to 448, sequence (d) encodes amino acid residues 153 to 162, sequence (e) encodes amino acid residues 1 to 53, and sequence (f) encodes amino acid residues 413 to 448 of the mature retinoic acid receptor-β polypeptide.

Pending Rejection

Claims 1 through 14, 24 through 34, 39 through 57, and 59 are pending in this application. These claims are rejected under 35 U.S.C. § 103 as unpatentable over Petkovich[2] in view of Hauptmann[3] and Krust[4].

Additional Patents Discussed by This Merits Panel

The following three U.S. patents are discussed by this merits panel:

Evans et al. (Evans '784)	4,981,784	Jan. 1, 1991
Evans et al. (Evans '671)	5,171,671	Dec. 15, 1992
Evans et al. (Evans '692)	5,571,692	Nov. 5, 1996

Discussion

The claimed invention involves a DNA sequence for what was first termed the hap gene. As explained at pages 8-9 of the specification:

> The hap protein (hap for hepatoma) exhibits strong homology with the human retinoic acid receptor (RAR) de Thé, H., Marchio, A., Tiollais, P. & Dejean, A. Nature 330, 667-670 (1987), Petkovich, M., Brand, N.J., Krust, A. & Chambon, P. Nature 330, 444-450 (1987), a receptor has been recently characterized Petkovich, M., Brand, N.J., Krust, A. & Chambon,

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[2] Petkovich et al. (Petkovich), "A human retinoic acid receptor which belongs to the family of nuclear receptors," Nature, vol. 330, no. 6147, pp. 444-50 (Dec. 3, 1987)

[3] Hauptmann et al. (Hauptmann), "A novel class of human type I interferons," Nucleic Acids Research, vol. 13, no. 12, pp. 4739-49 (July 1985)

[4] Krust et al. (Krust), "The chicken oestrogen receptor sequence: homology with v-erba and the human oestrogen and glucocorticoid receptors," The EMBO Journal, vol. 5, no. 5, pp. 891-97 (May 1986)

P. Nature 330, 444-450 (1987), Giguere, V., Ong, E.S., Segui, P. & Evans, R. M. Nature 330, 624-629 (1987). To test the possibility that the hap protein might also be a retinoid receptor, a chimaeric receptor was created by replacing the putative DNA binding domain of hap with that of the human oestrogen receptor (ER). The resulting hap-ER chimaera was then tested for its ability to trans-activate an oestrogen-responsive reporter gene (vit-tk-CAT) in the presence of possible receptor ligands. It was discovered that retinoic acid (RA) at physiological concentrations is effective in inducing the expression of this reporter gene by the hap-ER chimaeric receptor. See Nature, 332:850-853 (1988). This demonstrates the existence of two human retinoic acid receptors designated RAR-α and RAR-β.

As explained on pages 3-6 of the Examiner's Answer, the present rejection is premised upon the disclosure in Petkovich of the DNA sequence encoding RAR-α. Petkovich explains that a portion of the DNA sequence encoding RAR-α is highly homologous to a DNA sequence from a hepatocellular carcinoma disclosed in Dejean.[5] See explanation of Figure 3. Dejean, a named co-inventor this application, indicates that the hepatocellular carcinima DNA sequence contained an open reading frame of 519 nucleotides which contains an exon. The DNA sequence is referred to in Dejean as ORF and in Petkovich as hORF. The exon was used by the present inventors in their identification and isolation of the hap/RAR-β sequence claimed in this application. See page 12 of the present specification.

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[5] Dejean et al. (Dejean), "Hepatitis B virus DNA integration in a sequence homologous to v-erb-A and steroid receptor genes in a hepatocellular carcinoma," Nature, vol. 332, pp. 70-72 (July 3, 1986).

According to the examiner, it would have been obvious to one of ordinary skill in the art, armed with the knowledge gleaned from Petkovich as to the DNA sequence for RAR-α which is homologous to the exon identified in Dejean, to identify and isolate the DNA sequence encoding RAR-β using methods exemplified by Hauptmann and Krust. While the rejection is premised upon Petkovich, it appears that all relevant information of Petkovich which is relied upon by the examiner is also contained in Dejean.

Claims 1 through 6 of Evans '671, as issued, read as follows:

> 1. Substantially pure DNA encoding retinoic acid receptor wherein said retinoic acid receptor is structurally and functionally related to the steroid and thyroid hormone receptors.
>
> 2. Substantially pure DNA according to claim 1 wherein said retinoic acid receptor is human retinoic acid receptor.
>
> 3. Substantially pure DNA according to claim 2 wherein said human retinoic acid receptor is selected from the group consisting of human retinoic acid receptor alpha and human retinoic acid receptor beta.
>
> 4. Substantially pure DNA encoding protein which has harmone [sic}-binding and/or transcription-activating properties characteristic of retinoic acid receptor wherein said retinoic acid receptor is structurally and functionally related to the steroid and thyroid hormone receptors.
>
> 5. Substantially pure DNA according to claim 4 wherein said protein is human retinoic acid receptor.
>
> 6. Substantially pure DNA according to claim 5 wherein said human retinoic acid receptor is selected from the group consisting of human retinoic acid receptor alpha and human retinoic acid receptor beta.

Subsequent to the issuance of Evans '671, claims 3, 6, 9, 11, 12, 13, and 14 were disclaimed

Claims 1 and 2 of Evans '692 read as follows:

> 1. A substantially pure DNA molecule selected from the group consisting of:
> a DNA molecule which encodes a human retinoic acid receptor α protein, wherein said DNA has the sequence of DNA obtained from a human cDNA library, and wherein said DNA molecule hybridizes under stringent conditions with the complementary strand of the DNA molecule having the sequence shown in FIG. 1B-1, 1B-2, and 1B-3;
>
> a DNA molecule which encodes a polypeptide fragment of said protein, wherein said fragment comprises at least the DNA-binding domain or the ligand-binding domain of said receptor protein; and
>
> a DNA molecule degenerate with either of the preceding DNA molecules.
>
> 2. Substantially pure DNA according to claim 1, wherein said DNA encodes the amino acid sequence of human retinoic acid receptor alpha protein set forth in FIG. IB-1, IB-2 and IB-3.

As evident from a consideration of claims 1 through 6 of Evans '671, the Patent and Trademark Office at a previous point in time determined that DNA sequences encoding RAR-α and RAR-β are patentable. While Evans '671 disclaimed the claims which specifically recited DNA sequences encoding RAR-β, the generic claims which remain in Evans '671 are inclusive thereof.

Petkovich was published on December 3, 1987. It may or may not be prior art to Evans '671 depending upon whether Evans '671 is entitled to the benefit of the

December 2, 1987, filing date of the earliest parent application listed on the front of that patent under 35 U.S.C. § 120. Since the immediate parent application set forth on the cover of Evans '671 is stated to be a continuation-in-part application, it cannot be readily ascertained whether Evans '671 is entitled to the benefit of that earlier filing date.[6]

Thus, the examiner must first determine the effective filing date of the claims of Evans '671. If Evans '671 is not entitled to the December 2, 1987, filing date of the first-filed parent application, the pending rejection amounts to a rejection of claims in an issued U.S. patent since the generic claims are inclusive of DNA sequences encoding RAR-β. Such a rejection requires the approval of the group director. See the Manual of Patent Examining Procedure § 2307.02 (6th ed., rev. 3, July 1997). A similar issue may arise in regard to Evans '692. In part, claim 1 of Evans '692 is directed to a DNA molecule which encodes polypeptide fragments of RAR-α including the DNA-binding domain or the ligand-binding domain of the receptor protein. Per Petkovich and

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[6] It does not appear that the examiner has determined the effective filing date of the claims on appeal. Since several of the parent applications listed for this application are stated to be continuation-in-part applications, the examiner should make a claim-by-claim determination of the effective filing date of the claims pending in this application. Thereafter, on the basis of the determined effective filing date(s), the examiner should ensure that all relevant prior art has been ascertained and evaluated.

Dejean, it apears that DNA sequences of the present invention will hybridize in accordance with these claims.

If it is determined that Petkovich is not prior art to Evans '671, the examiner should determine whether he is still in effect rejecting claims in a U.S. patent since Dejean, which is prior art to Evans '671, appears to contain the same information contained in Petkovich relied upon in the extant rejection.

Upon return of the application, the examiner should consider the pending rejection under 35 U.S.C. § 103 in light of the claims issued in Evans '671 and Evans '692 and the issues discussed above. If the examiner remains of the opinion that the claims pending in this application are unpatentable, he should determine if that rejection amounts to a rejection of claims issued in a U.S. patent. If so, the examiner should reopen prosecution and issue an appropriate Office Action with the approval of the group director. If, however, the examiner's review of the matter leads him to now conclude that the rejection based upon Petkovich should be withdrawn and the claims are otherwise allowable, it would appear that a question of interference arises and the examiner should take appropriate action[7]

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[7] We make additional reference to Evans '784 because applicant added a claim to this application which they stated had been substantially copied from Evans '784. See Paper No. 16, filed January 2, 1992. The examiner withdrew claim 58 from consideration in Paper No. 21, mailed July 8, 1992.

As a final matter, we note that beginning with the Reply Brief, counsel has listed four additional co-inventors in the heading of each paper. It is not clear why counsel has done so since it does not appear that appellants requested that the inventorship of the application be changed. Appellants and the examiner should clarify this matter.

This application, by virtue of its "special" status, requires an immediate action. MPEP § 708.01(d). It is important that the Board be informed promptly of any action affecting the appeal in this case.

REMANDED

Sherman D. Winters)
Administrative Patent Judge)
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William F. Smith) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
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